ORIGINAL ARTICLE

Anti-cyclic citrullinated peptide antibody predicts functional disability in patients with rheumatoid arthritis in a large prospective observational cohort in Japan

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Abstract To clarify the clinical significance of anti-cyclic citrullinated peptide antibody (anti-CCP) in the long-term outcome of RA, we established a large observational cohort of RA patients (IORRA) in our institute beginning in 2000. Essentially all RA patients who consulted our institute were registered, and clinical parameters, including disease activity and drug use, were assessed biannually based on patient reports, physician examinations, and laboratory data. In the third phase (October 2001) of the IORRA survey, anti-CCP levels were measured in 1,226 RA patients. In a cross-sectional analysis, clinical variables were compared in anti-CCP-positive versus -negative patients and in RF-positive versus -negative patients. In a longitudinal analysis, subsequent progression of disability was analyzed in anti-CCP-positive versus -negative and in RF-positive versus -negative patients. A verified Japanese version of the Health Assessment Questionnaire (J-HAQ) was used to measure functional disability. In the cross-sectional analysis, anti-CCP-positive patients (84.2%) had a significantly longer disease duration and higher disease activity score and more frequently used corticosteroids and methotrexate compared to anti-CCP-negative patients statistically. Similar phenomena were noted between RF-positive and -negative patients. In contrast, the longitudinal analysis revealed that J-HAQ slopes—a measure of progression of functional disability—were strongly associated with anti-CCP positivity but not with RF positivity. In a linear regression model, J-HAQ scores significantly worsened in anti-CCP-positive patients compared to anti-CCP-negative patients at the third year (annual progression 0.0317, $P = 0.001$) and the fifth year (annual progression 0.0199, $P = 0.0012$); however, J-HAQ progression was not influenced by RF status. Anti-CCP is a better predictive and discriminative marker for progression of disability in the long-term outcome of RA patients compared to RF.

Keywords Anti-CCP antibody · Rheumatoid arthritis · Functional disability · Methotrexate · Prognosis

Introduction

The autoantibodies rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (anti-CCP) are used as serological markers in rheumatoid arthritis (RA) [1]. RF was the first autoantibody to be detected in RA patients, and it has been widely used in screening tests for patients with arthritis. The RF test is the only laboratory test used in the RA classification criteria of the American College of Rheumatology [2]. However, the specificity of RF for RA is not sufficient [3], although it has been recognized as a predictor of more severe structural joint damage [4–6].

Anti-perinuclear factor (APF) and anti-keratin antibody (AKA) have been described as filaggrin-reactive antibodies [7]. APF and AKA can be detected prior to the clinical onset of disease and are considered good diagnostic markers for RA [8, 9]. Schellekens et al. have shown that APF and AKA appear to recognize a similar epitope consisting of a citrullinated peptide [10, 11]. During the development of an enzyme-linked immunosorbent assay (ELISA) using a cyclic citrullinated peptide (CCP), the detected antibody was designated as anti-CCP [12]. Since anti-CCP is highly specific for the diagnosis of RA, particularly for early disease [1, 13], anti-CCP measurement

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has become widely used in regular RA clinical practice. Many reports have clarified that anti-CCP is associated with the susceptibility and severity of RA [5, 14–16]; however, the association between anti-CCP and long-term functional outcome of RA patients has not been well elucidated.

To clarify the clinical significance of anti-CCP and RF as predictive factors for long-term physical disability in RA patients, we analyzed the IORRA database, a prospective observational cohort study of Japanese RA patients.

Patients and methods

We have established a prospective observational cohort of RA patients who have been treated at the Institute of Rheumatology, Tokyo Women's Medical University, since October 2000, designated as the IORRA (Institute of Rheumatology, Rheumatoid Arthritis) cohort. This cohort has been previously described in detail [17–20]. Briefly, all RA patients diagnosed using ACR criteria [21] were registered after informed consent was obtained, and their clinical information was collected biannually (in April and in October) when they visited the outpatient clinic. Clinical information consisted of three major components: (1) physician evaluations, which included the number of tender joints and swollen joints and visual analog scale (VAS) score for disease activity (physician-VAS); (2) patient evaluations and information, which included VAS for pain (pain-VAS), VAS for general health (global-VAS), physical disability level using the Japanese version of the Health Assessment Questionnaire (J-HAQ) [22], height, body weight, comorbidities in the last 6 months, and drugs taken during the period; patients were instructed by the attending physician to answer these questions at home and mail responses back in a pre-stamped envelope within 2 weeks after their visit; and (3) patient laboratory data, including C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), RF titer, MMP-3, blood cell counts, transaminase levels, creatinine level, cholesterol level, and urinalysis results. Data collected from each component were integrated into one database for analysis. The disease activity score (DAS28) was calculated according to the original method [23].

Anti-CCP was measured in 1,226 RA patients randomly selected from 4,338 patients who participated in the third phase (October 2001) of the IORRA survey. Anti-CCP positivity was tested by ELISA (second-generation MESACUP CCP test, MBL, Aichi, Japan) with a cutoff point of 4.5 U/ml.

Statistical analysis

Baseline patient characteristics such as gender, age, and concomitant drugs used were summarized using frequency

or median and inter-quartile range (IQR). To cross-sectionally compare the demographic features between anti-CCP-positive and -negative RA patients and between RF-positive and -negative patients, Fisher's exact test for categorical variables and the Wilcoxon test for continuous variables were performed. To examine the longitudinal progression of J-HAQ scores, we used two statistical models. The first model was a 2-stage model that compared the group difference of each patient's J-HAQ slope in the anti-CCP-positive group and the anti-CCP-negative group, as well as in the RF-positive group and the RF-negative group. The J-HAQ slope for each patient was calculated using a standard linear regression model without any covariate adjustment, and the group difference of the J-HAQ slope was compared by the ANCOVA model with adjustment. Covariate adjustments were made for gender, age, RA duration, body mass index (BMI), DAS28, J-HAQ, non-steroidal anti-inflammatory drugs' (NSAIDs) use, corticosteroid use, methotrexate (MTX) use, bucillamine (BUC) use, and salazosulfapyridine (SASP) use. The second longitudinal model was the linear mixed model. Random effect was the intercept, and the functional form of the time trend was assumed to be linear. Differences between anti-CCP-positive and -negative patients and between RF-positive and -negative patients were tested by the interaction of group effect and time. Covariate adjustments were made for the same variables as in the 2-stage model. In this analysis, we transformed J-HAQ to log(J-HAQ+1) due to non-normality. Subgroup analyses using the linear mixed model were performed for MTX users, MTX non-users, corticosteroid users, and corticosteroid non-users, respectively. Statistical significance was set at 0.05, and all reported P-values were not adjusted for multiplicity. All calculations were done by R version 2.9.1 and SAS version 9.2.

Results

Patient characteristics

The baseline characteristics of the 1,226 RA patients are shown in Table 1. Women comprised 81.6% (n = 1,000) of the patient population, the median (IQR) age of patients was 59 (52–67) years, and the mean (IQR) disease duration was 10 (4–16) years. A total of 1,032 (84.2%) patients were anti-CCP-positive and 908 (74.1%) were RF-positive. The median (IQR) J-HAQ score at baseline was 0.6 (0.1–1.3).

Demographic features by anti-CCP or RF status

Differences in clinical features between anti-CCP-positive and -negative RA patients identified using a univariate analysis are shown in Table 2. A similar analysis was

Table 1 Baseline characteristics of 1,226 patients with rheumatoid arthritis

	Median (IQR) or n (%)
Total	1,226
Female (%)	1,000 (81.6)
Age (years)	59 (52–67)
BMI (kg/m^2)	21.2 (19.3–23.1)
Duration (years)	10 (4–16)
CRP (mg/dl)	0.7 (0.2–1.5)
ESR (mm/hr)	28.5 (16.3–49.4)
MMP-3 (ng/ml)	116 (63–215)
RF positive (%)	908 (74.1)
Anti-CCP positive (%)	1,032 (84.2)
DAS28	3.7 (2.8–4.5)
J-HAQ	0.6 (0.1–1.3)
Corticosteroid (%)	614 (50.0)
Prednisolone user's dose (mg/day)	4.3 (2.7–5.5)
NSAIDs (%)	916 (74.7)
DMARDs (%)	1,068 (87.1)
Methotrexate (%)	527 (43)
Methotrexate user's dose (mg/week)	6 (4–7.5)
Bucillamine (%)	319 (26)
Salazosulfapyridine (%)	246 (20.0)

IQR inter-quartile range, *Anti-CCP* anti-cyclic citrullinated peptide antibody, *NSAIDs* non-steroidal anti-inflammatory drugs, *DMARDs* disease-modifying antirheumatic drugs

performed in RF-positive versus -negative patients (Table 2). Compared to anti-CCP-negative patients, anti-CCP-positive patients had a significantly longer disease duration, higher CRP level, higher ESR, higher MMP-3 level, higher RF positivity (81.6%), higher DAS28, and higher J-HAQ score. Similar phenomena were observed in RF-positive versus RF-negative patients. In RF-positive patients, the prevalence of anti-CCP positivity (92.7%) was quite high. The frequencies of corticosteroid use and MTX use were higher in patients who were anti-CCP- or RF-positive compared to patients who were anti-CCP- or RF-negative.

Predictive factors for progression of physical disability

Trends in J-HAQ score over the 5 years after baseline (the third phase) without any adjustment are shown in Fig. 1. Figure 1 showed the trend in J-HAQ. Although J-HAQ scores increased constantly in RA patients regardless of anti-CCP or RF status, baseline J-HAQ scores in patients who were anti-CCP- or RF-positive were significantly higher than those in patients who were anti-CCP- or RF-negative. Differences in J-HAQ scores in patients who were anti-CCP-positive versus -negative were much higher than in those who were RF-positive versus -negative; thus,

anti-CCP appears to be more discriminative than RF with respect to J-HAQ progression.

We next compared the differences in progressive J-HAQ scores between RA patients who were anti-CCP-positive and -negative, as well as between those who were RF-positive and -negative, using statistical models. Using the 2-stage model, J-HAQ slopes were associated with anti-CCP positivity, and annual J-HAQ progression was 0.0317 ($P = 0.001$) at the third year and 0.0199 ($P = 0.012$) at the fifth year after adjustment of several factors, while J-HAQ slopes were not associated with RF status, even following adjustment of several factors (Table 3). These results indicate that anti-CCP-positive patients are most likely to be disabled compared to anti-CCP-negative patients at the third year and the fifth year after baseline (the third phase), whereas RF status does not have an impact on disability.

Using the linear mixed model, the trend of log(J-HAQ+1) was significantly worse in anti-CCP-positive patients compared to anti-CCP-negative patients ($P = 0.032$). However, no differences in log(J-HAQ+1) were identified between RF-positive and -negative patients ($P = 0.971$) (Table 4). This result indicates that anti-CCP is a better marker of subsequent progression of physical disability than RF. In a similar analysis conducted in RA patients treated with MTX, neither anti-CCP nor RF status was associated with subsequent progression of disability; however, in patients who did not receive MTX, anti-CCP positivity, but not RF positivity, was indicative of subsequent progression of disability ($P = 0.012$). In contrast, in patients treated with corticosteroids, anti-CCP, but not RF, predicted progression of disability ($P = 0.0193$), while neither anti-CCP nor RF status was associated with disability progression in patients who did not receive corticosteroids.

Discussion

The objective of our study was to investigate the clinical significance of anti-CCP and RF, particularly with respect to the prediction of progression of physical disability. Using J-HAQ score as a marker of physical disability, we successfully demonstrated that anti-CCP status is superior to RF status as a predictive marker for long-term disability in RA patients.

Many reports have demonstrated that anti-CCP-positive RA patients have higher disease activity and have disease that is more progressive with respect to joint destruction compared to anti-CCP-negative RA patients [16, 24, 25]. Among these studies, Kastbom A et al. demonstrated that DMARDs were more frequently prescribed to anti-CCP-positive RA patients than to anti-CCP-negative patients [26]. Our data also demonstrated that anti-CCP-positive RA patients have significantly higher disease activity and

Table 2 Comparison of clinical characteristics in the patients by anti-CCP and RF status

	Anti-CCP			RF		
	Positive Median (IQR) or n (%)	Negative Median (IQR) or n (%)	P	Positive Median (IQR) or n (%)	Negative Median (IQR) or n (%)	P
Total	1,032	194		908	318	
Female (%)	85.1 (82.5)	149 (76.8)	0.0692	736 (81.1)	264 (83.0)	0.5014
Age (years)	59 (52–67)	60 (51–66)	0.7112	59 (52–67)	60 (52.8–67)	0.4561
BMI (kg/m^2)	21.1 (19.2–23.0)	21.5 (19.7–23.3)	0.069	21.2 (19.2–23.1)	21.3 (19.5–22.9)	0.7108
Duration (years)	11 (5–16)	8 (3–13)	<.0001	11 (5–16)	9 (3–14)	<.0001
CRP (mg/dl)	0.8 (0.3–1.7)	0.3 (0.1–0.83)	<.0001	0.8 (0.3–1.8)	0.3 (0.1–1)	<.0001
ESR (mm/h)	31.4 (17.6–51.8)	19.4 (10.4–30.1)	<.0001	32.8 (18.8–53.3)	19.9 (11.2–35.2)	<.0001
MMP-3 (ng/ml)	123 (69–223)	81 (43–144.5)	<.0001	128 (69–232)	95 (52.5–157)	<.0001
RF positive (%)	842 (81.6)	66 (34.0)	<.0001			
Anti-CCP positive (%)				842 (92.7)	190 (59.8)	<.0001
DAS28	3.8 (3.0–4.7)	3.1 (2.3–3.9)	<.0001	3.9 (3.0–4.7)	3.2 (2.4–4.1)	<.0001
J-HAQ	0.6 (0.1–1.4)	0.4 (0–1)	0.0054	0.6 (0.1–1.4)	0.5 (0–1)	0.0011
Corticosteroid (%)	533 (51.7)	81 (41.8)	0.0123	476 (52.4)	138 (43.4)	0.0062
Prednisolone user's dose (mg/day)	4.4 (3–5.8)	4 (2.4–5)	0.0147	4.3 (3–5.6)	4.2 (2.3–5.2)	0.3106
DMARDs (%)	913 (88.5)	155 (79.9)	0.0022	799 (88.0)	269 (84.6)	0.1207
Methotrexate (%)	473 (45.8)	54 (27.8)	<.0001	432 (47.6)	95 (29.9)	<.0001
Methotrexate user's dose (mg/week)	6 (4–7.5)	6 (4–8)	0.5886	6 (4–7.5)	6 (4–8)	0.1600
Bucillamine (%)	273 (26.5)	46 (23.7)	0.4750	217 (23.9)	102 (32.1)	0.0048
Salazosulfapyridine (%)	212 (20.5)	34 (17.6)	0.3795	191 (21.0)	55 (17.3)	0.1668

IQR inter-quartile range, *Anti-CCP* anti-cyclic citrullinated peptide antibody
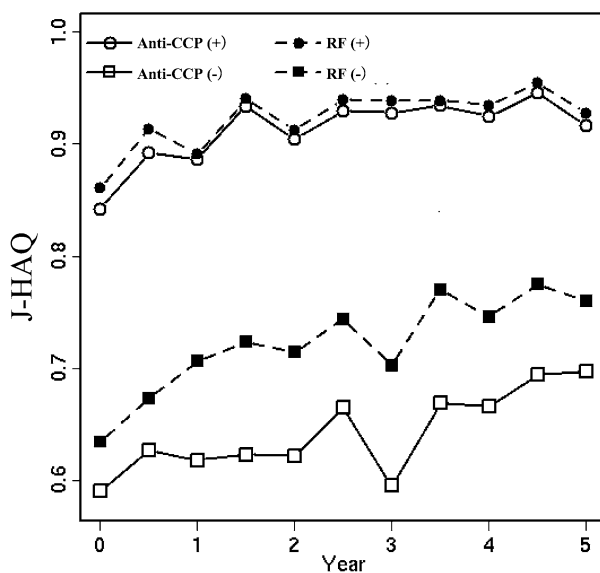
Anti-CCP; anti-cyclic citrullinated peptide antibody

Fig. 1 Trends in J-HAQ scores over 5 years

worse disability and are more frequently treated with DMARDs, particularly MTX, compared to anti-CCP-negative RA patients. It is noteworthy that anti-CCP was measured in a situation blinded to attending rheumatologists;

thus, anti-CCP data did not influence treatment decisions in this study. We believe that DMARDs were prescribed significantly more frequently to anti-CCP-positive patients due to the higher disease activity in these patients. RF is a widely accepted, established predictive marker of RA outcome [27, 28]. RF-positive patients were also found to have significantly higher disease activity and worse disability and were more likely to have received MTX compared to RF-negative patients.

In this report, we analyzed whether anti-CCP and RF could predict subsequent functional disability in a longitudinal analysis. Using linear regression analysis, we successfully demonstrated that anti-CCP positivity was a significant indicator of disability at the third year and at the fifth year after baseline (the third phase), whereas RF status was not. In the mixed-effect model, J-HAQ scores significantly progressed in anti-CCP-positive patients compared to anti-CCP-negative patients, but a similar phenomenon was not identified between RF-positive and -negative patients. These results indicate that subsequent progression of disability can be predicted by anti-CCP positivity but not by RF positivity. Despite several reports that have shown that anti-CCP-positive patients experienced more severe disease activity than anti-CCP-negative patients, many studies have failed to demonstrate a relationship between

Table 3 Linear regression analysis of J-HAQ progression at 1st, 3rd, and 5th year by anti-CCP and RF status

	Anti-CCP (1,032 vs. 194)*						RF (908 vs. 318)**					
	1st year		3rd year		5th year		1st year		3rd year		5th year	
	Estimate	P	Estimate	P	Estimate	P	Estimate	P	Estimate	P	Estimate	P
Positive group	0.0335	0.057	0.0317	0.001	0.0199	0.012	0.0004	0.976	0.0095	0.253	0.0108	0.109

Anti-CCP anti-cyclic citrullinated peptide antibody

* Number of patients with positive anti-CCP versus negative anti-CCP

** Number of patients with positive RF versus negative RF

Table 4 Linear mixed model of log(J-HAQ+1) over 5 years (longitudinal analysis)

	Anti-CCP				RF			
	Anti-CCP	N	Regression coef	P	RF	N	Regression coef	P
Total	Positive	1,032	0.00657	0.0320	Positive	908	0.00613	0.971
	Negative	194	0.00346		Negative	318	0.00617	
Methotrexate user	Positive	472	0.00480	0.6031	Positive	432	0.00467	0.965
	Negative	55	0.00359		Negative	95	0.00475	
Methotrexate non-user	Positive	557	0.00824	0.0102	Positive	476	0.00762	0.637
	Negative	142	0.00340		Negative	223	0.00687	
Corticosteroid user	Positive	532	0.00549	0.0193	Positive	476	0.00544	0.109
	Negative	82	0.00071		Negative	138	0.00274	
Corticosteroid non-user	Positive	497	0.00774	0.3369	Positive	432	0.00694	0.277
	Negative	115	0.00577		Negative	180	0.00875	

coef coefficient, *Anti-CCP* anti-cyclic citrullinated peptide antibody

anti-CCP and HAQ scores, even in cross-sectional analysis [29], with the exception of one analysis conducted by Inanc N et al. [24]. To date, no other longitudinal analyses have demonstrated a relationship between anti-CCP and progression of functional disability [26, 29, 30], presumably due to a lack of statistical power in such analyses, since the percentage of anti-CCP-negative patients is relatively small, particularly in the long-standing RA population. By taking advantage of the available data from a large number of patients who comprise the IORRA cohort, we believe that the present report provides important evidence about the significance of anti-CCP in the long-term outcome of RA patients.

Our subgroup analyses suggested that MTX use, but not corticosteroid use, could potentially overcome disability progression in anti-CCP-positive RA patients compared to anti-CCP-negative patients. These results strongly indicate that even in anti-CCP-positive RA patients who are likely to be more disabled, progression of physical disability may be prevented by active treatment with MTX, but not with corticosteroids. It is notable that this study was conducted before the frequent use of biologics; thus, further analysis of the ability of biologics to prevent long-term disability in anti-CCP-positive RA patients is required.

In conclusion, we have demonstrated that anti-CCP-positive RA patients tend to have more severe disease and a worse prognosis with respect to functional disability compared to anti-CCP-negative patients. Moreover, the poor prognosis of anti-CCP-positive patients may be improved by treatment with MTX, but not with corticosteroids. Thus, treatment of anti-CCP-positive RA patients must adhere to stricter guidelines to prevent worse functional outcomes of this chronic progressive disease.

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